

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-337

MEDICAL REVIEW

NDA 21,337
INVANZ

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Executive Summary

I. Recommendations

A. Recommendations on Approvability

Ertapenem sodium will be the first antimicrobial of the carbapenem class that can be dosed either intravenously or intramuscularly with a once daily administration schedule. However, the antimicrobial spectrum of activity provided by ertapenem has important limitations in comparison to the previously approved carbapenems (imipenem and meropenem) in that it will not provide adequate coverage for infections that are caused by *Pseudomonas* species, *Acinetobacter* species, or *Enterococcus* species (based on *in vitro* data).

Compared to the currently approved carbapenems, ertapenem appears to have an associated risk of the serious adverse event of seizure that is less than imipenem and similar to meropenem. As was predicted by pre-clinical animal data (rat studies and possibly monkey studies), ertapenem was associated with the development of neutropenia as an adverse event in the clinical studies conducted by the Applicant. The incidence of clinically significant neutropenia (<1000 cells/ μ L) occurring in patients receiving ertapenem 1 gm daily (0.6%) was slightly greater than in patients receiving the comparator drugs, piperacillin/tazobactam and ceftriaxone (0.3%) in the clinical studies; however, in clinical studies the neutropenia was not associated with any clinically significant adverse events. In regards to other adverse events that are commonly associated with beta-lactam antimicrobials, the incidence of diarrhea (including *Clostridium difficile* associated disease), nausea, vomiting, rash, abnormal liver function tests, and abnormal renal function tests was similar between ertapenem and the FDA approved drugs (piperacillin/tazobactam and ceftriaxone) to which it was compared in the clinical studies presented in this New Drug Application (NDA).

From a clinical perspective, based on the evidence provided by the Applicant, adequate efficacy and safety data have been provided to support approval of ertapenem sodium 1 gm once daily for the indications of: complicated intra-abdominal infections, complicated skin and skin structure infections, ~~community acquired pneumonia,~~ community acquired pneumonia, complicated urinary tract infections (including pyelonephritis), and acute pelvic infections (including postpartum endometriosis, septic abortion, and post surgical gynecologic infections).

B. Recommendations for Phase 4 Studies

The Medical Officer recommends that the Applicant perform the following Phase IV study and submit a full study report to the FDA for review:

A double-blind, randomized, statistically adequate study that assesses the death rate at the end of parenteral therapy and at 28 days post therapy in adult patients with complicated intra-abdominal infections. The purpose

of this study will be to further assess the trend (not statistically significant) for higher mortality that was seen in the ertapenem group in the Applicant's pivotal complicated intra-abdominal study (P017).

In addition, the Applicant should provide a full study report for the completed study (P035), "A Randomized, Double-Blind, Parallel-Panel, Placebo-Controlled Study to Investigate the Effects of Maximum Plasma Concentrations of MK-0826 on QTc Interval Following Single IV Dose Administration in Healthy Subjects" to the FDA for review.

If the Applicant wishes to further pursue an indication of complicated skin and skin structure infections that includes diabetic foot ulcers, then they should perform a double-blind, randomized, multicenter, statistically adequate study to assess the efficacy and safety of ertapenem 1 gm daily versus an approved comparator in adult patients with acutely infected diabetic foot ulcers and submit the results of this study to the NDA as an efficacy supplement.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Ertapenem sodium (MK-0826) is a new chemical entity of the carbapenem class of antimicrobials. ~~It is intended for parenteral use, either intravenously or intramuscularly, at a dose of 1 gram every 24 hours (a dosage adjustment is needed for patients with creatinine clearance <30 mL/min/1.73 m²).~~

The safety, tolerability, and pharmacokinetics of ertapenem were assessed in eleven Phase I studies (P001, P009, P010, P011, P012, P013, P015, P019, P026, P027, and P030) that enrolled 252 healthy subjects (220 subjects dosed with ertapenem and 32 subjects dosed with placebo). The safety and efficacy of ertapenem was further evaluated in five Phase IIa, double-blind, controlled clinical studies (P002, P003, P004, P007, and P008) and eight pivotal Phase IIb/III double-blind, controlled clinical studies (P014, P016, P017, P018, P020, P021, P023, and P029). The population studied in these Phase II and III studies included 3764 patients (2047 patients treated with ertapenem) with acute bacterial infections. The results of the seven pivotal Phase IIb/III studies submitted in this NDA are intended to support the indications of complicated skin and skin structure infections (P016), complicated intra-abdominal infections (P017), acute pelvic infections in women (P023), complicated urinary tract infections and pyelonephritis (P014 and P021), and community acquired pneumonia (P018 and P020). In addition, the results of the Phase IIb study P029, were submitted to support the safety and tolerability of intramuscular dosing as an alternate route of administration.

B. Efficacy

Complicated Intra-Abdominal Infections

The Applicant has provided adequate data to support granting the indication of "Complicated intra-abdominal infections" in adults, based on the demonstration of the non-inferiority of ertapenem 1 gm daily to an FDA approved comparator (piperacillin/tazobactam) for this indication (P017), and by providing additional supportive evidence of the efficacy of ertapenem in the treatment of acute pelvic infections (P023).

Complicated intra-abdominal infections are infections occurring in the peritoneal cavity that extend beyond the site of origin, resulting in peritonitis or abscess formation. An operative procedure or percutaneous drainage in addition to appropriate antimicrobial therapy is generally considered necessary to cure patients that present with complicated intra-abdominal infections. The Applicant's pivotal, double-blind, study of complicated intra-abdominal infections (P017) compared ertapenem 1 gm once daily to piperacillin/tazobactam 3.375 gms every 6 hours in 665 randomized patients (323 patients randomized to the ertapenem 1 gm group, 14 patients randomized to the ertapenem 1.5 gm group, and 328 patients randomized to the piperacillin/tazobactam group [310 with the 1 gm ertapenem cohort and 18 with the 1.5 gm ertapenem cohort]). Patients were stratified at study entry by primary diagnosis (complicated appendicitis without generalized peritonitis versus all other diagnoses) and the APACHE II score (≤ 15 versus > 15). The primary efficacy endpoint for this study was the proportion of microbiologically evaluable patients in the 1 gm cohort who had both a favorable clinical and a favorable microbiological response assessment at the Test-of-Cure visit (4 to 6 weeks posttherapy). The following table displays the results of the primary analysis, according to the Reviewing Medical Officer, by stratum.

Clinical and Microbiologic Success Rate at Test of Cure Displayed by Site of Infection Strata and APACHE II Score Strata for Microbiologically Evaluable Patients with Complicated Intra-Abdominal Infections (P017) According to the Medical Officer

Stratum	Ertapenem		Piperacillin/Tazobactam		95% CI
	%	n/m	%	n/m	
Complicated Appendicitis [‡] , APACHE II score ≤ 15	89.7	78/87	88.6	78/88	-9.3%, 11.4%
Complicated Appendicitis [‡] , APACHE II score > 15	100	2/2	100	3/3	-41.7%, 41.7%
All Other Diagnoses, APACHE II score ≤ 15	80.0	80/100	72.5	66/91	-5.6%, 20.6%
All Other Diagnoses, APACHE II score > 15	50	3/6	71.4	5/7	-89.1%, 46.2%
Overall	83.6	163/195	80.4	152/189	-5.0%, 11.4%

[‡] Without generalized peritonitis.

n/m = Number of patients with favorable assessment/number of patients with assessment.

CI = Confidence interval.

The difference in the overall combined clinical and microbiologic response rates in the microbiologically evaluable population at TOC was 3.2% with a 95% CI of (-5.0%, 11.4%) and in the microbiologic modified intent-to-treat (MITT) population was 3.0% with a 95% CI of (-5.4%, 11.5%). Therefore, the results indicate that ertapenem 1 gm daily was non-inferior to piperacillin/tazobactam 3.375 gm every 6 hours in this population of patients with complicated intra-abdominal infections.

Acute Pelvic Infections (including postpartum endomyometritis, septic abortion, and post surgical gynecologic infections)

The Applicant has provided adequate data to support granting the indication of "Acute pelvic infections (including postpartum endomyometritis, septic abortion, and post surgical gynecologic infections)" in adults, based on the demonstration of the non-inferiority of ertapenem 1 gm daily to an FDA approved comparator (piperacillin/tazobactam) for this indication (P023), and by providing additional supportive evidence of the efficacy of ertapenem in the treatment of complicated intra-abdominal infections (P017).

Acute pelvic infections include endomyometritis (an infection of the lining of the uterus and the myometrium that may occur following cesarean section or vaginal delivery), pelvic infection following hysterectomy or other pelvic procedure, septic abortion, and parametritis, pelvic phlegmon, or pelvic abscess (that may occur as a complication of endomyometritis, post surgical pelvic procedures or septic abortion). Gynecologic infections that are not considered a part of this indication include: abdominal wall incision infection, vulvar abscess, Bartholin gland abscess, pyometra, and pelvic inflammatory disease. The Applicant's pivotal, double-blind, study of acute pelvic infections (P023) compared ertapenem 1 gm once daily to piperacillin/tazobactam 3.375 gms every 6 hours in 412 randomized patients (216 patients randomized to the ertapenem 1 gm group and 196 patients randomized to the piperacillin/tazobactam group). Patients were stratified at study entry by primary diagnosis (obstetric/postpartum infection including septic abortion versus postoperative gynecologic infection). The primary efficacy endpoint for this study was the proportion of clinically evaluable patients who had a favorable clinical response assessment at the Test-of-Cure visit (2 to 4 weeks posttherapy). The following table displays the results of the primary analysis, according to the Applicant, by stratum.

Clinical Success Rate at Test of Cure Displayed by Stratum for Clinically Evaluable Patients Acute Pelvic Infections (P023) According to the Applicant

Stratum	Ertapenem		Piperacillin/Tazobactam		95% CI
	n/m	%	n/m	%	
Obstetric/postpartum Infection*	129/137	94.2	121/132	91.7	-4.4%, 9.4%
Postoperative gynecologic infection	23/25	92.0	19/21	90.5	-19.3%, 22.4%
Overall	153/163	93.9	140/153	91.5	-4.0%, 8.8%

* Includes patients with septic abortion.

n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

The difference in the combined overall clinical response rate in the clinically evaluable population at TOC was 2.4% with a 95% CI of (-4.0%, 8.8%) and in the clinical modified intent-to-treat (MITT) population was 1.8% with a 95% CI of (-9.7%, 6.1%). Therefore, the results indicate that

ertapenem 1 gm daily was non-inferior to piperacillin/tazobactam 3.375 gm every 6 hours in this population of patients with acute pelvic infections.

Community Acquired Pneumonia

The Applicant has provided adequate data to support granting the indication of "Community acquired pneumonia" in adults, based on the demonstration of the non-inferiority of ertapenem 1 gm daily to an FDA approved comparator (ceftriaxone) for this indication in two studies (P018 and P020).

Community acquired pneumonia is an acute infection of the lung that is associated with respiratory signs and symptoms and the presence of a new infiltrate on a chest radiograph in a patient that has not recently been or is not currently hospitalized or a resident of a long-term care facility. Based on *in vitro* data, ertapenem was not predicted to provide adequate coverage for pathogens considered to be "atypical" (i.e. Legionella, mycobacteria, mycoplasma, etc.), but was predicted to provide adequate coverage for sensitive strains of bacteria that are considered "typical" bacterial pathogens in patients with community acquired pneumonia. Therefore the Applicant designed their studies to support this indication with inclusion and exclusion criteria that would exclude most patients with "atypical" community acquired pneumonia. The Applicant performed two studies, comparing ertapenem 1 gm daily to ceftriaxone 1 gm daily, in support of this indication. In both studies, Investigators had the option to switch the patient's therapy to oral amoxicillin/clavulanate after at least 3 days of parenteral study therapy, provided the patient had met pre-specified criteria demonstrating adequate clinical improvement.

The first study was a double-blind, randomized, multicenter study (P018) of patients with community acquired pneumonia that randomized 502 patients (244 patients randomized to the ertapenem 1 gm group and 258 patients randomized to the ceftriaxone group). Patients were stratified at study entry by age (≤ 65 years versus > 65 years) and by Pneumonia Severity Index (PSI ≤ 3 versus PSI > 3). The primary efficacy endpoint for this study was the proportion of clinically evaluable patients who had a favorable clinical response assessment at the Test-of-Cure visit (7 to 14 days post antimicrobial therapy). The following table displays the results of the primary analysis, according to the Applicant, by stratum.

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**Clinical Success Rate at Test of Cure Displayed by Stratum for
Clinically Evaluable Patients with Community Acquired Pneumonia (P018)
According to the Applicant**

Protocol	Stratum	Ertapenem		Piperacillin/Tazobactam		95% CI
		n/m	%	n/m	%	
018	Age ≤65, PSI ≤3	92/101	91.1	100/108	92.6	(-9.9, 6.9)
	Age >65, PSI ≤3	36/37	97.3	34/36	94.4	(-9.0, 14.7)
	Age ≤65, PSI >3	9/9	100	15/18	83.3	(-8.8, 4.2)
	Age >65, PSI >3	31/35	88.6	34/39	87.2	(-16.1, 19.0)
	Overall	168/182	92.3	183/201	91.0	(-4.8, 7.3)

PSI = Pneumonia Severity Risk score.

n/m = Number of patients with favorable assessment/number of patients with assessment.

CI = Confidence interval.

The difference in the overall clinical response rate in the clinically evaluable population at TOC was 1.3% with a 95% CI of (-4.8%, 7.3%) and in the clinical modified intent-to-treat (MITT) population was -2.1% with a 95% CI of (-9.4%, 5.3%).

The second study was a double-blind, randomized, multicenter study (P020) of patients with community acquired pneumonia that randomized 364 patients (239 patients randomized to the ertapenem 1 gm group and 125 patients randomized to the ceftriaxone group). Patients were stratified at study entry by age (≤65 years versus >65 years) and by Pneumonia Severity Index (PSI ≤3 versus PSI >3). The primary efficacy endpoint for this study was the proportion of microbiologically evaluable patients who had a favorable clinical response assessment at the Test-of-Cure visit (7 to 14 days post antimicrobial therapy). The following table displays the results of the primary analysis, according to the Applicant, by stratum.

**Clinical Success Rate at Test of Cure Displayed by Stratum for
Microbiologically Evaluable Patients with Community Acquired Pneumonia (P020)
According to the Applicant**

Protocol	Stratum	Ertapenem		Piperacillin/Tazobactam		95% CI
		n/m	%	n/m	%	
020	Age ≤65, PSI ≤3	47/50	94.0	22/22	100.0	(-15.9, 3.9)
	Age >65, PSI ≤3	17/19	89.5	10/11	90.9	(-30.3, 27.6)
	Age ≤65, PSI >3	9/12	75.0	3/4	75.0	(-)
	Age >65, PSI >3	18/19	94.7	10/12	83.3	(-18.7, 41.6)
	Overall	91/100	91.0	45/49	91.8	(-11.5, 10.4)

PSI = Pneumonia Severity Risk score.

n/m = Number of patients with favorable assessment/number of patients with assessment.

CI = Confidence interval.

The difference in the overall clinical response rate in the clinically evaluable population at TOC was 0.8% with a 95% CI of (-11.5%, 10.4%) and in the clinical modified intent-to-treat (MITT) population was -2.6% with a 95% CI of (-15.9%, 10.8%).

Based on the overall results of these two studies, the Applicant has demonstrated adequately that ertapenem 1 gm daily was non-inferior to ceftriaxone 1 gm daily in these populations of patients with community acquired pneumonia.

Complicated Skin and Skin Structure Infections

The Applicant has provided adequate data to support granting the indication of "Complicated skin and skin structure infections" (b)(4)

(b)(4)

Complicated skin and skin structure infections are infections either involving soft tissues or those that require significant surgical interventions. Examples of such infections include: infected ulcers, burns, and major abscesses. Skin and skin structure infections that occur in patients with certain underlying disease states (i.e. diabetes mellitus, vascular insufficiency, etc.) may also be considered complicated. In addition, superficial infections or abscesses in an anatomical site (i.e. rectal area) where the risk of anaerobic or Gram-negative pathogen involvement is higher, should also be considered complicated infections. Skin and skin structure infections that are considered to be uncomplicated and that are not included in this indication include simple abscesses, impetiginous lesions, furuncles, and cellulitis. The Applicant's pivotal, double-blind, study of complicated skin and skin structure infections (P023) compared ertapenem 1 gm once daily to piperacillin/tazobactam 3.375 gms every 6 hours in 540 randomized patients (274 patients randomized to the ertapenem 1 gm group and 266 patients randomized to the piperacillin/tazobactam group). Patients were stratified at study entry by underlying disease state (Stratum I, which included patients with complicating disease states such as diabetes mellitus and neuropathy versus Stratum II, which included patients with all other diagnoses of complicated skin and skin structure infections). The primary efficacy endpoint for this study was the proportion of clinically evaluable patients who had a favorable clinical response assessment at the Test-of-Cure visit (10 to 21 days posttherapy). The following table displays the results of the primary analysis, according to the Applicant, by stratum.

Clinical Success Rate at Test of Cure Displayed by Stratum for Clinically Evaluable Patients with Complicated Skin and Skin Structure Infections (P016) According to the Medical Officer

Stratum	Ertapenem		Piperacillin/Tazobactam		95% CI
	n/m	%	n/m	%	
Stratum I	16/26	61.5	23/31	74.2	(-40.4, 15.1)
Stratum II	125/142	88.0	122/139	87.8	(-8.1, 8.6)
Overall	141/168	83.9	145/170	85.3	(-9.7, 6.9)

n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

The difference in the combined overall clinical response rate in the clinically evaluable population at TOC was -1.4% with a 95% CI of (-9.7%, 6.9%) and in the clinical modified intent-to-treat (MITT) population was -1.6% with a 95% CI of (-10.1%, 6.8%). Therefore, the results indicate that ertapenem 1 gm daily was non-inferior to piperacillin/tazobactam 3.375 gm every 6 hours in this population of patients with complicated skin and skin structure infections.

Therefore the indication granted will be for complicated skin and skin structure infections alone.

Complicated Urinary Tract Infections including Pyelonephritis

The Applicant has provided adequate data to support granting the indication of "Complicated urinary tract infections including pyelonephritis" in adults, based on the demonstration of the non-inferiority of ertapenem 1 gm daily to an FDA approved comparator (ceftriaxone) for this indication in two studies (P014 and P021).

Complicated urinary tract infections include infections of the kidney parenchyma (pyelonephritis) and lower urinary tract infections that develop in patients with urologic abnormalities or in association with indwelling urinary tract catheters. Urinary tract infections that are considered to be uncomplicated and that are not included in this indication include cystitis in patients with no known underlying renal or urologic dysfunction or obstruction. The Applicant performed two studies, comparing ertapenem 1 gm daily to ceftriaxone 1 gm daily, in support of this indication. In both studies, Investigators had the option to switch the patient's therapy to oral ciprofloxacin after at least 3 days of parenteral study therapy, provided the patient had met pre-specified criteria demonstrating adequate clinical improvement.

The first study was a double-blind, randomized, multicenter study (P014) of patients with complicated urinary tract infections including pyelonephritis that randomized 592 patients (298 patients randomized to the ertapenem 1 gm group and 294 patients randomized to the ceftriaxone group). Patients were stratified at study entry by diagnosis (acute pyelonephritis versus other complicated urinary tract infections). The primary efficacy endpoint for this study was the proportion of microbiologically evaluable patients who had a favorable microbiological response assessment at the Test-of-Cure visit (5 to 9 days post antimicrobial therapy). The following table displays the results of the primary analysis, according to the Applicant, by stratum.

**Microbiological Success Rate at Test of Cure Displayed by Stratum for Microbiologically
Evaluable Patients with Complicated Urinary Tract Infections (P014)
According to the Medical Officer**

Protocol	Stratum	Ertapenem		Ceftriaxone		95% CI
		n/m	%	n/m	%	
014	Acute Pyelonephritis	69/73	94.5	71/75	94.7	(-8.8, 8.5)
	Other Complicated Urinary Tract Infections	72/81	88.9	84/91.3	91.4	(-12.5, 7.7)
	Overall	141/154	91.6	155/167	92.8	(-7.8, 5.3)

n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

The difference in the overall microbiologic response rate in the microbiologically evaluable population at TOC was -1.2% with a 95% CI of (-7.8%, 5.3%) and in the microbiological modified intent-to-treat (MITT) population was 4.3% with a 95% CI of (-2.7%, 10.5%).

The second study was a double-blind, randomized, multicenter study (P021) of patients with complicated urinary tract infections including pyelonephritis that randomized 258 patients (175 patients randomized to the ertapenem 1 gm group and 83 patients randomized to the ceftriaxone group). Patients were stratified at study entry by diagnosis (acute pyelonephritis versus other complicated urinary tract infections). The primary efficacy endpoint for this study was the proportion of microbiologically evaluable patients who had a favorable microbiological response assessment at the Test-of-Cure visit (5 to 9 days post antimicrobial therapy). The following table displays the results of the primary analysis, according to the Applicant, by stratum.

**Microbiological Success Rate at Test of Cure Displayed by Stratum for Microbiologically
Evaluable Patients with Complicated Urinary Tract Infections (P021)
According to the Applicant**

Protocol	Stratum	Ertapenem		Ceftriaxone		95% CI
		n/m	%	n/m	%	
021	Acute Pyelonephritis	45/52	86.5	25/28	89.3	(-20.2, 14.7)
	Other Complicated Urinary Tract Infections	38/45	84.4	20/25	80.0	(-17.6, 26.5)
	Overall	83/97	85.6	45/53	84.9	(-12.7, 14.0)

n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

The difference in the overall microbiologic response rate in the microbiologically evaluable population at TOC was 0.7% with a 95% CI of (-12.7%, 14.0%) and in the microbiological modified intent-to-treat (MITT) population was 3.7% with a 95% CI of (-10.3%, 17.7%).

Based on the overall results of these two studies, the Applicant has adequately demonstrated that ertapenem 1 gm daily was non-inferior to ceftriaxone 1 gm daily in these populations of patients with complicated urinary tract infections including pyelonephritis.

C. Safety

Phase I Adverse Experiences

In Phase I studies, 220 subjects were exposed to ertapenem in doses ranging from 100 mg to 3 gms daily for up to 15 days. Overall, clinical adverse experiences occurred in 62.3% of ertapenem subjects and 34.4% of placebo subjects. Drug related clinical adverse experiences occurred in 40.0% of ertapenem subjects and 15.6% of placebo subjects. Five percent of ertapenem subjects and no placebo subjects were discontinued from study drug due to an adverse experience. No subjects experienced serious adverse experiences. The most common adverse experiences occurring in ertapenem subjects were diarrhea (23.6%), headache (22.3%), nausea (15.9%), dizziness (7.7%), somnolence (6.8%), and abdominal pain (5.0%). Diarrhea (18.6%), headache (12.7%), and nausea (12.7%) were the most frequently occurring adverse experiences that were considered drug-related by Investigators. The incidence of diarrhea, nausea, headache, and somnolence appeared to be more frequent at ertapenem doses greater than 1 gm daily.

The most common laboratory adverse experiences reported by Investigators (reported based on the Investigator's judgement of its clinical importance) were increased ALT (2.8%) and increased AST (1.4%). When safety laboratories were assessed based on predefined clinically significant laboratory abnormalities (CSLAs), elevations in liver function tests in ertapenem subjects appeared to be mild (1 ertapenem subject with ALT >2.5 x ULN, but less than >5 x ULN, no subjects with total or direct bilirubin >2.5 x ULN, and no subjects with alkaline phosphatase >5 x ULN). Three ertapenem subjects developed absolute neutrophil counts that ranged from 500 to 1000 cells/ μ L, transiently.

Phase II/III Adverse Experiences

In Phase II/III studies, 1954 patients were exposed to the ertapenem 1 gm daily dose for a mean of 5.4 days (range 1 to 28 days). Adverse experiences were monitored during the parenteral therapy period and for 14 days after completion of all study therapy (parenteral therapy alone or parenteral plus oral therapy in those protocols in which an oral switch was allowed). Overall, clinical adverse experiences occurred in 57.7% of ertapenem 1 gm subjects and 61.2% of comparator subjects (piperacillin/tazobactam and ceftriaxone were used as comparators). Drug related clinical adverse experiences occurred in 22.7% of ertapenem 1 gm patients and 25.2% of comparator patients. In the ertapenem 1 gm group, 5.2% (1.7% drug-related) of patients were discontinued from study drug due to an adverse experience. In the comparator group, 5.8% (1.5% drug-related) of patients were discontinued from study drug due to an adverse experience. Serious adverse experiences occurred in 10.7% (1.1% drug-related) of patients in the ertapenem 1 gm group and 11.0% (0.4% drug-related) in the comparator group. The serious adverse experience of death occurred in 1.8% of patients in the ertapenem 1 gm group and 1.6% of patients in the comparator

group. Overall deaths appear balanced across treatment groups; however, there was an imbalance in deaths in the pivotal intra-abdominal study (P017) in the ertapenem 1 gm group that was most pronounced during the parenteral therapy only period. Therefore, until the incidence of death in patients with complicated intra-abdominal infections treated with ertapenem is further studied the Medical Officer recommends that death data from study 017 be presented in the label.

The most common adverse experiences occurring in ertapenem patients were diarrhea (9.7%), nausea (7.3%), vomiting (3.9%), headache (6.3%), and infused vein complication (6.1%). Diarrhea (5.5%), infused vein complication (3.7%), nausea (3.1%), and headache (2.2%) were the most frequently occurring adverse experiences in the ertapenem 1 gm group that were considered drug-related by Investigators. Overall the incidence of common adverse experiences and drug-related adverse experiences were similar between the ertapenem 1 gm group and the comparator group. While the incidence of diarrhea and *Clostridium difficile* related disease were similar between patients in the 1 gm group and the comparator group, standard antimicrobial class warnings (relating to pseudomembranous colitis and *C. difficile* related disease) should be included in the "Warnings" section of the label.

The Applicant considered the incidence of seizure and rash to be adverse experiences of special interest, due to the known association of seizures with other carbapenem antimicrobials and rash/allergic reactions with beta-lactam antibiotics in general. Seizure related events occurred in 0.5% of patients in the ertapenem 1 gm group and 0.1% of patients receiving comparator drugs, suggesting, that like previously marketed carbapenems the associated risk of seizure may be higher with ertapenem than with beta-lactam antibiotics in general. As is found in the labels of the other FDA approved carbapenems, a specific warning statement regarding seizure potential should be included in the ertapenem "Warnings" and "Precautions" sections of the label. While the incidence of rash/allergic reactions was similar between patients in the 1 gm group and the comparator group, standard beta-lactam class warnings (relating to hypersensitivity reactions) should also be included in the "Warnings" section of the label.

The most common laboratory adverse experiences reported by Investigators (reported based on the Investigator's judgement of its clinical importance) were increased ALT (8.5% in the ertapenem 1 gm group and 7.1% in the comparator group), increased AST (7.6% in the ertapenem 1 gm group and 7.3% in the comparator group), increased alkaline phosphatase (5.2% in the ertapenem 1 gm group and 4.8% in the comparator group), and increased platelet count (5.2% in the ertapenem 1 gm group and 4.8% in the comparator group). When safety laboratories were assessed based on predefined clinically significant laboratory abnormalities (CSLAs), increased AST >2.5 x ULN and >5 x ULN occurred in 5.8% and 1.6%, respectively, of patients in the ertapenem 1 gm group and in 4.6% and 0.5%, respectively, of patients in the comparator group. The CSLA, absolute

neutrophil count (ANC) <1800 cells/uL occurred in 4.3% of ertapenem 1 gm patients and 2.7% of comparator patients. Absolute neutrophil count <1000 cells/uL occurred in 0.6% of ertapenem 1 gm patients and 0.3% of comparator patients. Although the higher incidence of ANC <1000 cells/uL in the ertapenem group was small, given that this is a potentially serious adverse event and that pre-clinical data are unclear as to the likelihood for ertapenem to cause significant neutropenia in humans, the Medical Officer recommends that neutropenia be addressed in the label. The remainder of CSLA findings were similarly distributed across the ertapenem 1 gm group and the comparator group.

Based on safety and tolerability data from the Applicant's Phase II/III program, ertapenem administered intravenously for up to 14 days or intramuscularly for up to 7 days was as well tolerated as comparator drugs.

With the exception of probenecid, which was studied in a co-administration Phase I study, ertapenem is not known to have a significant potential for drug-drug interactions. An examination of adverse experiences occurring in the Phase II/III by concomitant therapy, did not suggest that drug-drug interactions occurred.

D. Dosing

Based on the demonstration of the non-inferiority of ertapenem to the FDA approved comparators utilized in the pivotal clinical studies in adults, ertapenem 1 gm intravenously once daily appears to provide adequate antimicrobial coverage for treatment of the requested indications. In Phase IIa studies and for a limited number of patients in P017 (Phase IIb complicated intra-abdominal infections study) doses of 1.5 gm and/or 2 gm once daily were evaluated. There did not appear to be an efficacy advantage at the higher doses and the incidence of both clinical and laboratory adverse experiences were higher in the groups receiving doses more than 1 gm daily.

Based on pharmacokinetic data, the bioavailability of ertapenem 1 gm administered intramuscularly is approximately 90% that of 1 gm administered intravenously over 30 minutes. Based on pharmacodynamic modeling, IM dosing is predicated to provide adequate time above the MIC (MIC of 4.0 ug/mL) to adequately treat infections caused by sensitive organisms for the indications sought by the Applicant. While the Applicant has not provided a statistically adequate clinical study to demonstrate the efficacy of IM administration of ertapenem, they have provided a safety database for >100 patients (derived from P020, P021, and P029) that received IM ertapenem. The safety database supports the conclusion that ertapenem 1 gm IM once daily for up to 7 days is at least as well tolerated as ceftriaxone 1 gm IM once daily in adults.

The pharmacokinetics of a single 1 gm dose of ertapenem administered intravenously were investigated in 26 adult subjects with varying degrees of renal impairment. Based on the results of this study the Applicant has proposed that the dose of ertapenem should be reduced to 500 mg once daily in patients

with creatinine clearance ≤ 30 mL/min/1.73 m². For patients on hemodialysis a supplementary 150 mg postdialysis dose is recommended if ertapenem is given within 6 hours prior to hemodialysis. (See section on Special Populations)

Dosage recommendations for pediatric patients can not be made at this time. (see section on Special Populations)

E. Special Populations

Male and female patients were both well represented in the Applicant's clinical studies database. There were no clinically significant differences identified in safety or efficacy outcomes by gender.

Patients greater than age 65 were well represented in the Applicant's clinical study database accounting for 26% of patients studied. Efficacy rates were similar in patients <65 years and ≥ 65 years. As might be expected in an older population that has a greater number of co-morbid conditions and a higher frequency of concomitant medication use, the frequencies of adverse experiences were often increased in patients ≥ 65 years. However, the increased frequencies of specific adverse events appeared to be balanced across the ertapenem 1 gm and combined comparator groups, suggesting that no signal was present in the data base to suggest that ertapenem specific drug toxicity was increased in patients ≥ 65 years.

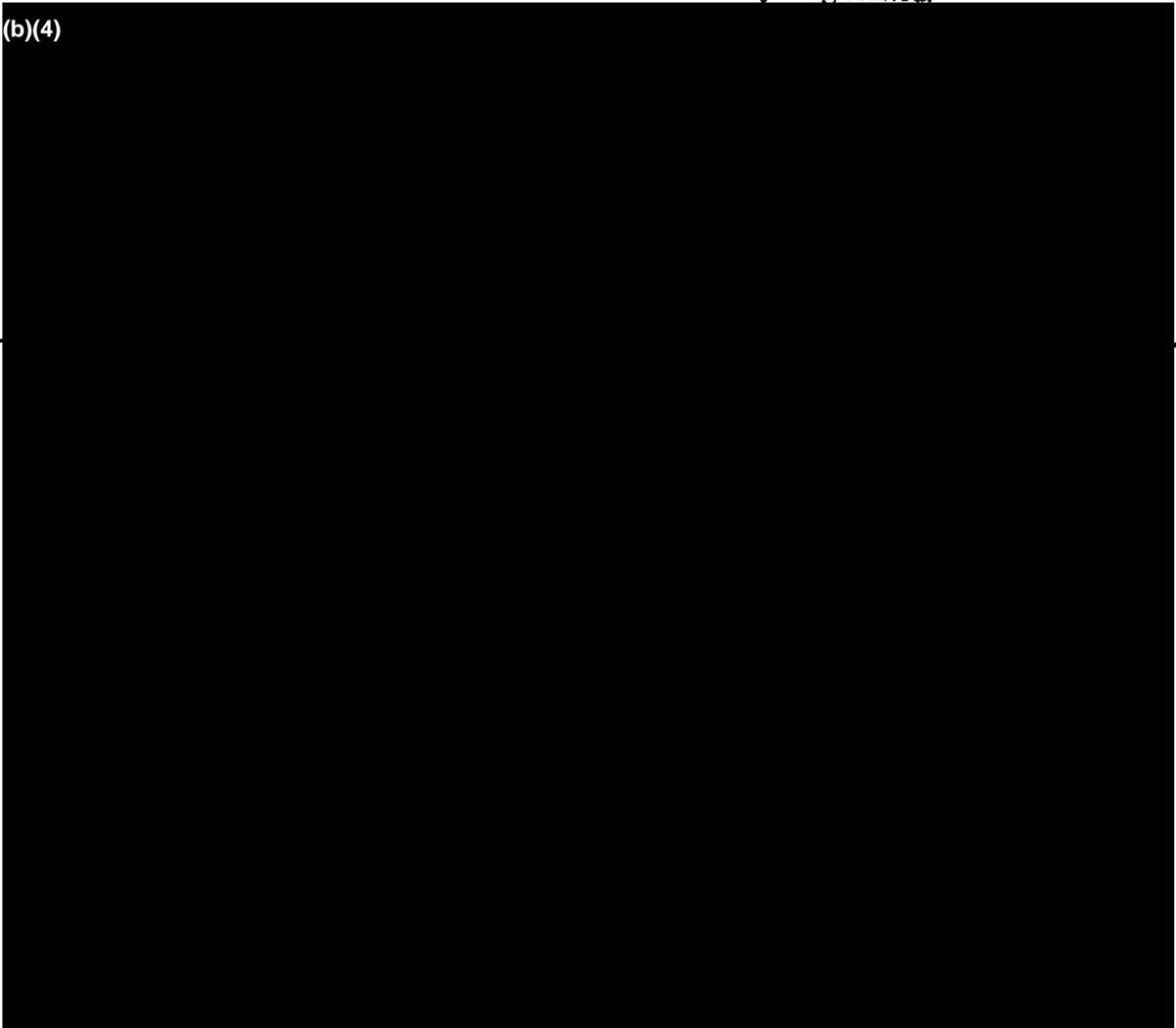
The majority of subjects in the Applicant's Phase I studies had their race identified as Caucasian (62.3%) or Black (17.9%), therefore limited data are available regarding the pharmacokinetics and pharmacodynamics of ertapenem in other races. The majority of patients in the Applicant's Phase II and III studies had their race identified as Caucasian (53.2%), Hispanic (23.6%), or Black (12.9%), therefore limited data are available regarding the efficacy and safety of ertapenem in other races. Efficacy rates were similar among the racial groups. With the exception of a slightly higher incidence of serum AST greater than five times the upper limit of normal in Hispanic patients, the incidence of adverse experiences were also similar among racial groups.

The Applicant reviewed clinical and laboratory adverse experiences for 689 patients in the Phase IIb and Phase III studies with renal dysfunction (defined as creatinine clearance < 60 mL/min/1.73 m²). As might be expected in a population with renal impairment that has a greater number of co-morbid conditions and a higher frequency of concomitant medication use, the frequencies of adverse experiences were often increased in patients with creatinine clearance < 60 mL/min/1.73 m². However, the increased frequencies of specific adverse events appeared to be balanced across the ertapenem 1 gm and combined comparator groups, suggesting that no signal was present in the data base to suggest that ertapenem specific drug toxicity was increased in patients with with creatinine clearance < 60 mL/min/1.73 m².

The Applicant has not conducted a Phase I study in subjects with hepatic impairment. However, less than 10% of an intravenously administered dose is recovered in feces and based on *in vitro* studies, ertapenem does not appear to undergo hepatic metabolism.

There are no clinical studies in pregnant women treated with ertapenem. A single pregnant woman who inadvertently received ertapenem 1 gm daily in the complicated skin and skin structure infections study (P016). This woman experienced a spontaneous abortion while receiving ertapenem therapy. The Investigator considered the spontaneous abortion to be study drug related.

(b)(4)



Clinical Review

I. Introduction and Background

1.1 Background

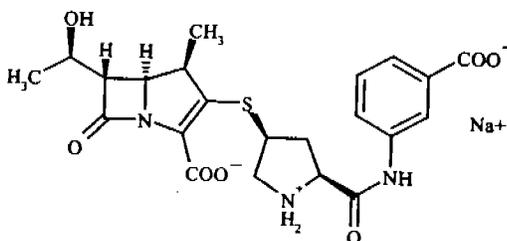
Applicant: Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point, PA 19486-0004

Contact
Michelle W. Kloss, Ph.d.
Senior Director
Regulatory Affairs
(610) 397-2905

NDA Filing Date: November 30, 2000

The established drug name for the compound originally designated, MK-0826 by the Applicant is ertapenem sodium. The trade name proposed by the Applicant is "INVANZ™"

Chemically, INVANZ is described as [4R-[3(3S*,5S*),4 α ,5 β ,6 β (R*)]]-3-[[[5-[[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0] hept-2-ene-2-carboxylic acid monosodium salt. Its molecular weight is 497.50. The empirical formula is C₂₂H₂₄N₃O₇SNa, and its structural formula is:



The Applicant has proposed that ertapenem be approved for the treatment of the following infections, in adult patients (≥ 18 years):

- **Complicated Intra-abdominal Infections** (at a dose of 1 gm once daily for 5 to 14 days).
- **Complicated Skin and Skin Structure Infections** (at a dose of 1 gm once daily for 7 to 14 days).
- **Community Acquired Pneumonia** (at a dose of 1 gm once daily for 10 to 14 days, in which duration includes a possible switch to an

appropriate oral therapy once clinical improvement has been demonstrated).

- **Complicated Urinary Tract Infections including pyelonephritis** (at a dose of 1 gm once daily for 10 to 14 days, in which duration includes a possible switch to an appropriate oral therapy once clinical improvement has been demonstrated).
- **Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections** (at a dose of 1 gm once daily for 3 to 10 days).

In patients whose creatinine clearance is ≤ 30 mL/min/1.73 m², including patients on hemodialysis, the dose should be reduced to 500 mg given once daily. When patients on hemodialysis are given the recommended daily dose of 500 mg of ertapenem within 6 hours prior to hemodialysis, a supplementary dose of 150 mg should be given following hemodialysis.

The Applicant has proposed that ertapenem may be administered by intravenous infusion (infused over a period of 30 minutes) or intramuscular injection (reconstituted in 1.0% lidocaine HCl for injection).

1.2 State of Armamentarium

The following table displays a listing of those antimicrobial classes in which there is at least one currently approved antimicrobial for the treatment of those infectious disease indications being sought by the Applicant. For all indications being sought by the Applicant there are currently multiple therapeutic options.

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Indication	Classes of Antimicrobials For Which Currently FDA Approved Products Are Available For the Indication*
Complicated Intra-abdominal Infections	<ul style="list-style-type: none"> • Aminoglycosides • Monobactam • Cephalosporins • Flouroquinolones • Clindamycin • Metronidazole • Carbapenems • Anti-Pseudomonal Penicillins • Penicillin/Beta-Lactamase Inhibitor Combinations
Complicated Skin and Skin Structure Infections	<ul style="list-style-type: none"> • Aminoglycosides • Monobactam • Cephalosporins • Flouroquinolones • Macrolides • Clindamycin • Metronidazole • Carbapenems • Anti-Pseudomonal Penicillins • Anti-Pseudomonal Penicillin/Beta-Lactamase Combination • Penicillin/Beta-Lactamase Inhibitor Combinations • Streptogramin • Oxazolidinone
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Community Acquired Pneumonia	<ul style="list-style-type: none"> • Aminoglycosides • Monobactam • Cephalosporins • Flouroquinolones • Macrolides • Clindamycin • Metronidazole • Penicillins • Penicillin/Beta-Lactamase Inhibitor Combinations • Carbapenem • Anti-Pseudomonal Penicillins • Anti-Pseudomonal Penicillin/Beta-Lactamase Combinations
Complicated Urinary Tract Infections -including pyelonephritis	<ul style="list-style-type: none"> • Trimethoprim/sulfamethoxazole • Aminoglycosides • Monobactam • Cephalosporins • Flouroquinolones • Penicillins • Penicillin/Beta-Lactamase Inhibitor Combinations • Anti-Pseudomonal Penicillins • Anti-Pseudomonal Penicillin/Beta-Lactamase Combinations • Carbapenem
Acute Pelvic Infections / - postpartum endomyometritis -septic abortion -post surgical gynecologic infections	<ul style="list-style-type: none"> • Clindamycin • Metronidazole • Monobactam • Cephalosporins • Carbapenem • Anti-Pseudomonal Penicillin/Beta-Lactamase Combinations
<p>* The specific wording for indications granted for products in the listed classes has varied over time.</p>	

1.3 Regulatory History

- August 3, 1995 [redacted] for MK-0826 (subsequently named ertapenem sodium, tradename: INVANZ) submitted.
- July 23, 1997 Teleconference between Sponsor and FDA in which MK-0826 development program was discussed (types and numbers of studies needed and possibility of IV to oral switch protocols discussed).
- November 1997 A series of telephone contacts between the Sponsor's and FDA's regulatory staffs regarding the potential of the Sponsor pursuing an "acute bacterial pneumonia" indication. The Sponsor was informed that it was the division policy to grant indications for "community acquired pneumonia" or "hospital acquired pneumonia," not for a combined indication.
- June 15, 1998 Teleconference between the Sponsor and FDA in which protocol designs for the community acquired pneumonia and complicated urinary tract infections protocols were discussed.
-
- July 8, 1998 End of Phase II meeting between the Sponsor and FDA representatives. The Sponsor's Phase IIb/III pivotal study plan was discussed. The possibility of intramuscular (IM) dosing was also discussed and the FDA agreed that if the Sponsor's preliminary IM pharmacokinetic data was supported in final analyses, then a safety and tolerability database of 100 patients would provide sufficient data on which to base a regulatory decision regarding IM dosing.
- July 13, 1998 Chemistry, manufacturing, and controls (CMC) End of Phase II meeting between the Sponsor and FDA representatives.
- September 15, 1998 Teleconference between the Sponsor and FDA representatives to discuss criteria for parenteral to oral switch in those protocols using this design option. The appropriate comparator for use in the Sponsor's hospital acquired pneumonia study was also discussed.
- March 11, 1999 Teleconference between the Sponsor and FDA representatives to discuss statistical issues regarding pneumonia studies, possibility of oral switch for hospital acquired pneumonia study, unblinding procedures, and plans to submit data analysis plans.
- March 12, 1999 Teleconference between the Sponsor and FDA representatives to discuss CMC issues concerning stability data.

- October 15, 1999 Telephone conversation between Sponsor's and FDA's regulatory staffs in which FDA's accepted Sponsor's plan not to conduct warfarin or digoxin interaction studies.
- August 17, 1999 Teleconference between the Sponsor and FDA representatives to discuss CMC issues concerning stability data.
- November 3, 1999
December 21, 1999 (b)(4)
- January 28, 2000 Teleconference between the Sponsor and FDA representatives to discuss data analysis plans for protocols 014, 021, and 018.
- February 2, 2000 Pre-NDA meeting between the Sponsor and FDA representatives. Format of NDA, as well as pediatric development plans and potential deferral discussed. Dr. Murphy clarified difference between what would be expected of the Sponsor to fulfill their requirements under the Pediatric Final Rule versus what might be required in a Written Agreement.
-
- February 10, 2000 Sponsor submitted a prompt for a Pediatric Written Request and a revised pediatric development plan.
- April 14, 2000 Teleconference between the Sponsor and FDA representatives to discuss CMC issues concerning stability data.
- May 15, 2000 A Written Request for Pediatric Studies was issued to the Sponsor. The request required submission of all Final Study Reports for requested studies on or before November 30, 2004.
- September 22, 2000 Sponsor notified FDA that INVANZ™ had been adopted as the global trademark for MK-0826 (ertapenem sodium) and requested review by the FDA.
- November 30, 2000 Applicant submitted NDA 21,337 for review. (User Fee of [redacted] previously submitted on November 3, 2000.) NDA on 10 month review clock with due date of September 30, 2001.
- July 3, 2001 Applicant submits major amendment to NDA (results of Protocol 029) for review, resulting in extension of review clock to November 30, 2001.

1.4 Other Relevant Information

The Applicant has submitted applications for approval in Australia, Malaysia, New Zealand, Singapore, Bolivia, Russia, Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, United Kingdom, Switzerland, Argentina,

Canada, and Turkey. They have recently received approval for the indications sought in this NDA in Mexico and Brazil. A new drug application for this product has not been withdrawn in any country.

1.5 Pharmacologically Related Agents

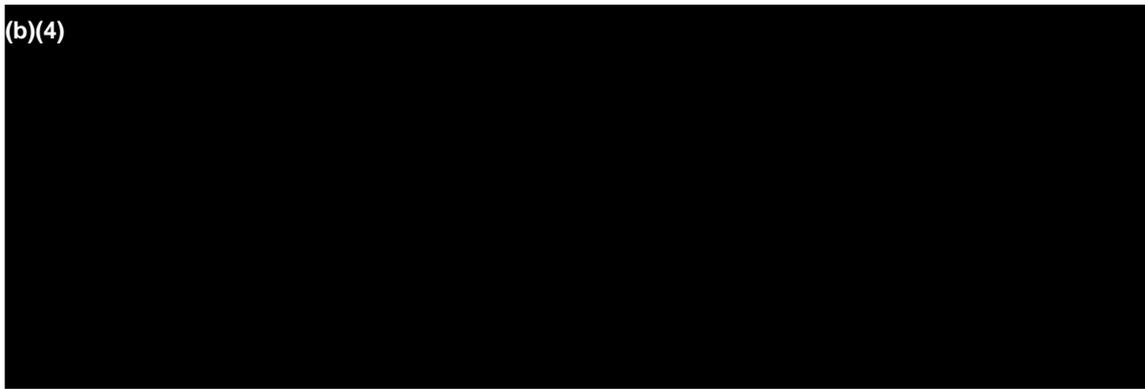
There are currently four other penem antimicrobial drug products with active NDAs and/or INDs under review. These products are summarized below.

NDA 50,587 and NDA 50,630

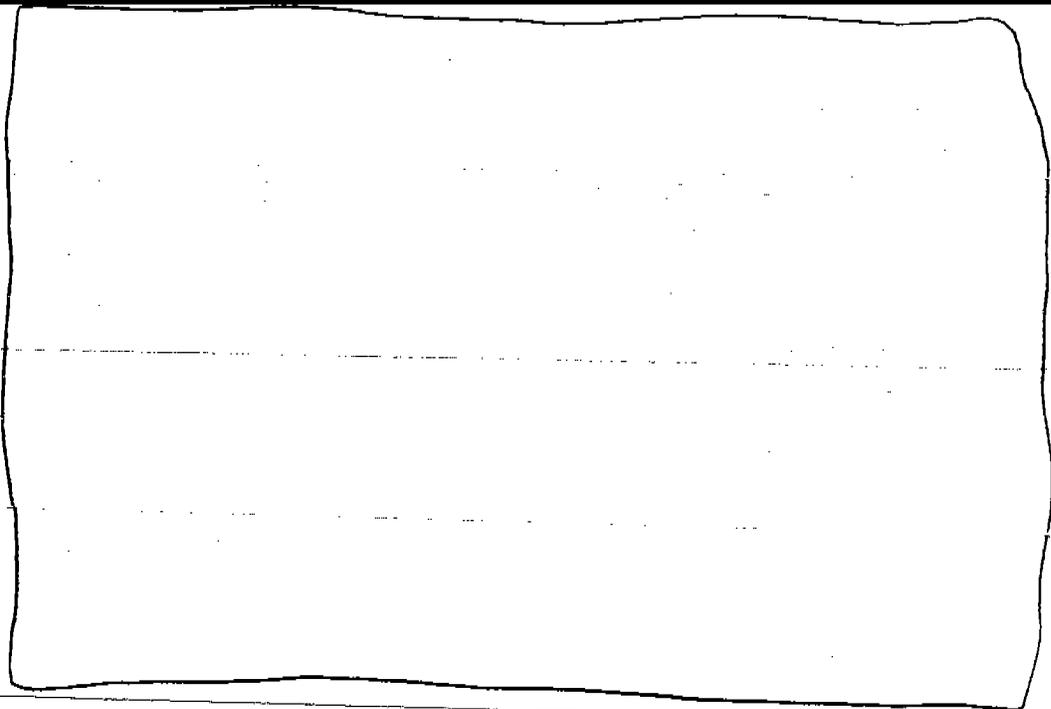
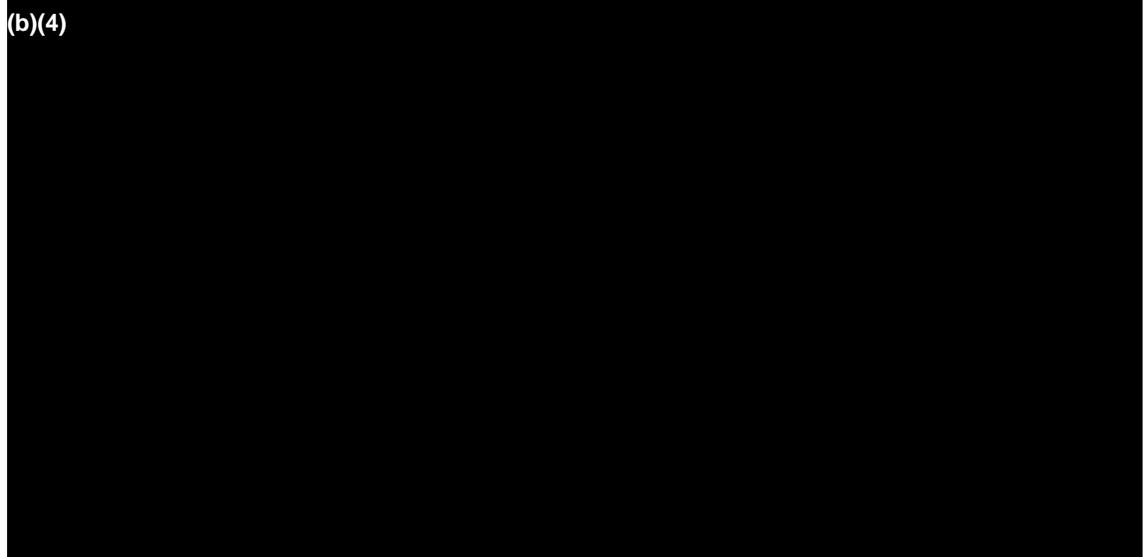
Imipenem (Primaxin supplied by Merck), available for intravenous or intramuscular administration, received FDA approval in 1985. Imipenem is currently approved for the indications of "lower respiratory tract infections", "urinary tract infections (complicated and uncomplicated)", "intra-abdominal infections", "gynecologic infections", "bacterial septicemia" (due to *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains), *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, *Serratia* species, *Bacteroides* species including *B. fragilis*), "bone and joint infections", "skin and skin structure infections", "endocarditis", and "polymicrobial infections" [including those in which *S. pneumoniae* (pneumonia, septicemia), *S. pyogenes* (skin and skin structure), or nonpenicillinase-producing *S. aureus* is one of the causative organisms].

While imipenem has been associated with safety concerns common to most beta-lactam antimicrobials (e.g., diarrhea, nausea, liver function abnormalities, increased creatinine, etc.), notably its use has also been associated with seizures and other central nervous system (CNS) adverse experiences, such as confusional states and myoclonic activity. Although in the imipenem safety database, CNS adverse experiences occurred most commonly in patients with underlying CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function, there were reports of CNS events in patients with no known underlying CNS disorders or renal impairment. In the Primaxin I.V. label "seizures" are reported with an incidence of 0.4% (reported as possibly, probably, or definitely related adverse clinical reactions). Of note, the label for imipenem includes the listing of "pancytopenia, bone marrow depression, thrombocytopenia, neutropenia, leukopenia, ..." in the Adverse Reactions section of the label.

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II. Clinically Relevant Findings from Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and OPDRA

2.1 Chemistry

Please see the Chemistry review of NDA 21,337 prepared by Dr. Vethal Shetty for a full review of the chemistry and manufacturing contents submitted by the Applicant. Dr Shetty has recommended that due to the "extreme instability of the drug product" that information in the label on timeframes for use of the reconstituted drug product be bolded. The Applicant accepted this recommendation in their August 1, 2001 submission to the NDA.

2.2 Toxicology

Please see the Pharmacology/Toxicology review of NDA 21,337 prepared by Dr. Kenneth Seethaler for a full review of the pharmacology/toxicology data submitted by the Applicant. Based on Dr. Seethaler's review, pertinent findings from the preclinical data and recommendations made by Dr. Seethaler include:

- Treatment-related neutropenia occurred at every dose tested (2, 10, 30, 60, 75, 180, 225, 540, and 675 mg/kg) in the multiple-dose studies, in rats. (This corresponds to a dose of approximately 12 milligrams per square meter of body surface area. For humans, the proposed therapeutic dose is one gram daily, or about 15-20 mg/kg/day. This corresponds to a dose of approximately 600 milligrams per square meter of body surface area. Thus, the dose proposed for humans is 10 to 50 times greater than the dose that was toxic to rats.) No compensatory increase in immature neutrophils or effect on the bone marrow was seen. The neutrophil decreases were not dose-related and did not progress over time. When dosing was discontinued neutrophil counts began to recover, but were not fully recovered by the end of the studies. Neutropenia was reversed by administration of granulocyte-colony stimulating factor.
- The potential for development of neutropenia was also investigated in monkeys treated with ertapenem (including juvenile animals) and slight decreases in neutrophil counts appeared to occur.
- Based on the incidence of neutropenia seen in the preclinical data, Dr. Seethaler has recommended that a warning statement be added to the label to specifically address the risk of ertapenem-induced neutropenia.
- Other blood cell types (erythrocytes, platelets, monocytes, total leukocytes) were slightly decreased in some studies, but the incidences of these decreases were sporadic.
- Increases in urinary urobilinogen levels occurred in rats.
- Minimal increases in serum ALT, AST, cholesterol, triglycerides, and urea nitrogen occurred in rabbits, and some rabbits had red-colored urine that tested positive for occult blood.
- In monkeys, serum ALT and triglycerides were elevated, liver and kidney weights were increased, and some microscopic changes were seen in the renal proximal tubules.

- Gastrointestinal effects, such as diarrhea and unformed stools, were described in the rabbit and monkey studies, and these effects were thought to be due to antibiotic-induced alteration of the gastrointestinal flora.
- Based on preclinical studies (rat intracisternal model), ertapenem is believed to have less seizure potential than imipenem.
- In mice, at the highest dose studied (700 mg/kg/day) MK-0826 was associated with decreased fetal weights and decreases in the average number of ossified sacrocaudal vertebrae. In rats receiving 700 mg/kg/day, there were two fetuses in one litter, with visceral (cardiovascular) abnormalities, and one fetus in another litter with skeletal abnormalities. However, the other 20 rat litters were not affected and it is not known if the effects seen in the three described fetuses were treatment related.
- The effects of MK-0826 on heart rates and Q-T intervals have not been reported.
- MK-0826 has not been tested in any phototoxicity, photocarcinogenicity, or carcinogenicity studies. Because MK-0826 has an ultraviolet absorbance maximum at 294 nanometers, Dr. Seethaler believes it may be associated with a risk of phototoxic effects and has recommended that patients receiving this drug be monitored for signs of sensitivity to sunlight.

2.3 Microbiology

Please see the Microbiology review of NDA 21,337 prepared by Dr. Sousan Altaie for a full review of the microbiological documentation submitted by the Applicant. Comments and recommendations made by Dr Altaie that are pertinent to this review include:

- Like other β -lactams, ertapenem blocks bacterial cell-wall synthesis by binding to specific penicillin binding proteins (PBPs). In competitive binding studies, ertapenem was shown to bind strongly to PBPs 1a, 1b, 2, 3, 4, and 5. Like imipenem, ertapenem displayed high binding affinity for PBP 2 and 3 of *E. coli*.
- Studies in animal experimental infection models indicate that, as with other β -lactam antibiotics, time above the MIC is the most reliable predictor of ertapenem efficacy *in vivo*.
- Based on the *in vitro* susceptibility profile of ertapenem, the efficacy of ertapenem in animal models of infection, PK/PD data from animal studies and Phase I clinical studies, and clinical/microbiological efficacy data from patients enrolled in the Applicant's Phase II and III studies, the FDA Microbiology review team has set the *in vitro* susceptibility interpretive criteria displayed in the following table.

Organism	Ertapenem Interpretive Criteria*					
	Dilution Method MIC (µg/mL)			Disk Diffusion Method Zone Diameter (mm)		
	S	I	R	S	I	R
Anaerobes	≤4.0	8.0	≥16.0	--	--	--
Enterobacteriaceae and <i>Staphylococcus</i> spp.	≤2.0	4.0	≥8.0	≥19	16-18	≤15
<i>Streptococcus pneumoniae</i>	≤1.0**	--	--	≥19***	--	--
Other streptococci	≤1.0****	--	--	≥19*****	--	--
<i>Haemophilus</i> spp.	≤0.5	--	--	≥19	--	--

Only the Dilution method interpretive criteria applies to anaerobes. The Disk Diffusion Interpretive criterion does not apply to anaerobes.

** Alternatively, test penicillin by MIC, Susceptible to ertapenem if penicillin MIC ≤0.06 µg/mL

*** Alternatively, use 1-µg oxacillin, Susceptible to ertapenem if oxacillin zone ≥20 mm, if oxacillin zone ≤19 do ertapenem MIC

**** Alternatively, test penicillin by MIC, susceptible to ertapenem if penicillin MIC ≤0.12 µg/mL

***** Alternatively for β-hemolytic *Streptococcus* spp., perform disk test with 10-unit penicillin disk, susceptible to ertapenem if penicillin zone ≥24 mm. Penicillin disk diffusion interpretive criteria are not available for viridans group streptococci.

2.4 Statistics

Please see the Statistical reviews of NDA 21,337 prepared by Dr. Joel Jiang (for all indications with the exception of community acquired pneumonia) and Dr. George Rochester (for the community acquired pneumonia indication) for full reviews of the statistical documentation submitted by the Applicant.

2.5 Office of Drug Risk Assessment

The Applicant provided limited pre-clinical data evaluating the effect of ertapenem on heart rate or the QT interval. To further explore the potential for carbapenems to cause increased QTc, the FDA review team requested that OPDRA investigate the incidence of adverse events reported in the Medwatch system for the currently marketed carbapenems. Dr. Ronald Wassell, OPDRA, performed the requested review. In his review, he compared the incidence of QTc related adverse events (in the AERS database) associated with the use of the currently marketed carbapenem class drugs (imipenem and meropenem) to beta lactam controls (ceftriaxone and piperacillin/tazobactam). Dr. Wassell concluded that "given the length of time these products have been on the market and the amount of usage they have received, the lack of quality reports would appear to indicate that there is no signal for QTc related adverse events associated with the use of the currently marketed carbapenem class drugs (imipenem and meropenem)."

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III. Human Pharmacokinetics and Pharmacodynamics

Please see the Biopharmaceutics review of NDA 21,337 prepared by Dr. Charles Bonapace for a full review of pharmacokinetic/pharmacodynamic documentation submitted by the Applicant. Dr. Bonapace's conclusions regarding the pharmacokinetics of ertapenem sodium are stated below.

- MK-0826 exhibits nonlinear pharmacokinetics within the therapeutic dosing range. Unbound MK-0826 AUCs increased greater-than dose proportional, whereas total MK-0826 AUCs increased less-than dose proportional following single IV doses ranging from 0.25 gm to 3 gm IV.
- MK-0826 is approximately 94% protein bound, primarily to albumin. Two classes of binding sites have been identified, of which the tighter binding site likely represents a single binding site on albumin. Thus, MK-0826 illustrates saturable protein binding within the therapeutic range. Differences in the extent of protein binding have also been observed between male and female subjects, as well as between young and elderly subjects.
- The mean volume of distribution of unbound MK-0826 ranged from _____ whereas the volume of distribution of total MK-0826 ranged from _____
- The primary mechanism of elimination is glomerular filtration and active transport in the proximal tubule of the kidney. Approximately 80% of an administered dose is excreted in the urine, half of which is metabolized by dihydropeptidase-1 in the renal tubules to the inactive ring-opened metabolite L-774183.
- The mean plasma half-life in healthy young adults is approximately 4 hours and the plasma clearance is approximately 1.8 L/hour.
- The absolute bioavailability of a single 1 gm dose of MK-0826 administered IM is 90% (90% confidence interval 0.870 to 0.934) compared to 1 gm administered IV.
- Following a single 1gm IV dose of MK-0826 in patients with advanced renal impairment, the $AUC_{0-\infty}$ of total MK-0826 increased 200%, whereas the $AUC_{0-\infty}$ of unbound MK-0826 increased 335%. The plasma clearance of patients with advanced renal impairment was 33% and 23% for total and unbound MK-0826, respectively, compared to healthy young subjects.
- Age was shown to significantly impact the pharmacokinetics of MK-0826. Following the administration of 1 gm IV, the renal clearance in elderly healthy subjects (65 years or older) was only 68% of young healthy subjects. Consequently, elderly subjects were associated with a 37% increase in total $AUC_{0-\infty}$ and 67% increase in unbound $AUC_{0-\infty}$ compared to young subjects. The increased exposure of elderly patients was associated with a reduction in creatinine clearance.
- MK-0826 appears to be neither a substrate nor inhibitor of the CYP P450 isozymes (1A2, 2C9, 2C19, 2D6, 2E1, 3A4) or p-glycoprotein at concentrations approximately equivalent to a single 2 gm IV dose.

- A modest increase in MK-0826 plasma exposure measures (AUC and concentration at the end of infusion, C_{coi}) were observed when co-administered with probenecid. Probenecid 500 mg q6h for three days increased the $AUC_{0-\infty}$ and C_{coi} of a single 1 gm IV dose of MK-0826 by 73% and 37%, respectively.
- Plasma concentrations of total MK-826 equivalent to a 1 gm dose IV resulted in an 8 to 9% increase in the unbound concentration of warfarin *in vitro*.
- The sponsor characterized the *in vivo* pharmacodynamic activity of MK-0826 in animal models with a variety of pathogens and determined that the pharmacodynamic parameter most associated with efficacy was the time that serum concentration remained above the MIC. This is consistent with the literature evaluating the exposure response relationship of β -lactams. The minimal time above the MIC of total MK-0826 concentrations varied by organism, but it appears that less than 50% may be required under most circumstances.

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IV. Description of Clinical Data and Sources

4.1 Data Sources

The primary source data used in the clinical review were derived from the original submission and subsequent amendments to NDA 21,337.

4.2 Tables Listing Clinical Trials

A summary of all Phase I clinical pharmacology studies is displayed in the following table.

Summary of Ertapenem Clinical Pharmacology Studies

Protocol	Study Description	Total Number of Subjects Enrolled (N=252)	Total Number of Subjects Dosed With Ertapenem* (N=220)	Placebo (N=32)	Duration of Drug Administration (Days)
001	Single/multiple rising dose	66	50	16	1 to 15
009	Dose proportionality	16	16	0	4
010	Pharmacokinetics in elderly	15	15	0	1 and 7
011	Pilot intramuscular administration	11	9	2	2
012	Radiolabelled disposition	7	7	0	1
013	14-day intravenous safety	24	20	4	14
015	Pharmacokinetics in renal insufficiency	26	26	0	1 to 2
019	Intramuscular/intravenous administration comparison	26	22	4	10
026	Levels in skin blister fluid	13	13	0	3
027	Effect of probenecid	14	14	0	2
030	Multiple-dose intramuscular safety	34	28	6	3

* Ertapenem includes subjects who received ertapenem alone (N=206) and with probenecid (N=14).

(Applicant's Table E-1, Volume 2 of 22, page E-17)

A summary of the Applicant's Phase IIa, IIb, and III clinical study program is displayed in the following table.

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Summary of Ertapenem Clinical Studies

Protocol (CRF Visit Cutoff Date)	Indication	Phase	Total Pts	Number of Treated Patients							CTX	P/T	Therapy Options			Intended Therapy Duration (Days)		Complete Study Duration (Weeks)
				ETP				Switch to Oral	Switch to IM Ertapenem Therapy	Parenteral Therapy			Total Study Therapy					
				1 g	1.5 g	2 g	Any Dose											
				A/C	Cipro													
002/008 (12-Dec- 1997/26- Jan-1998)	Lower respiratory tract infections	IIa	85	28	--	30	58	27	--	X	--	--	3 to 14	7 to 14	6			
003 (06-Jan- 1998)	Skin and skin structure infections	IIa	26	15	--	--	15	11	--	X	--	--	3 to 14	10 to 14	8			
004 (09-Oct- 1998)	Intra-abdominal infections	IIa	216	57	50	--	107	109	--	--	X	--	3 to 14	7 to 14	10			
007 (14-Jan- 1998)	Urinary tract infections	IIa	33	19	--	--	19	14	--	--	X	--	3 to 14	10 to 14	8			
014 (01-Mar- 2000)	Urinary tract infections	IIb	582	293	--	--	292	289	--	--	X	--	3 to 14	10 to 14	8			
016 ^{††} (01-Jun- 2000)	Skin and skin structure infections	IIb	529	271	--	--	271	--	258	--	--	--	7 to 14	7 to 14	5			
017 ^{††} (29-Jun- 2000)	Intra-abdominal infections	IIb	655	316	14	--	330	--	325	--	--	--	5 to 14	5 to 14	8			
018 [‡] (21-May- 2000)	Community- acquired pneumonia	IIb	498	242	--	--	242	256	--	X	--	X	3 to 14	10 to 14	6			
020 ^{‡‡} (24-Jul- 2000)	Community- acquired pneumonia	III	359	236 [*]	--	--	236 [*]	123 [*]	--	X	--	X	3 to 14	10 to 14	6			
021 [‡] (15-Mar- 2000)	Urinary tract infections	III	258	175 [*]	--	--	175 [*]	83 [*]	--	--	X	X	3 to 14	10 to 14	8			
023 ^{††} (14-Jul- 2000)	Pelvic infections	III	406	214	--	--	214	--	192	--	--	--	3 to 10	3 to 10	6			
029 (28-Nov- 2000)	Intramuscular Administration	IIb	117	87	--	--	87	30	--	X	--	X	2 to 14	3 to 14	4			

[†] Parenteral only studies.

[‡] Includes patients with dose adjustments due to renal insufficiency.

^{‡‡} Patients receiving 2-g therapy in the Phase IIb and Phase III community-acquired pneumonia studies are counted in the ertapenem 1-g treatment group.

^{*} Includes patients who received intramuscular doses in addition to intravenous doses.

ETP = Ertapenem. CTX = Ceftriaxone any dose, intravenous or intramuscular. P/T = Piperacillin/tazobactam. A/C = Amoxicillin/clavulanate. CRF = Case report form. Cipro = Ciprofloxacin. IM = Intramuscular.

4.3 Postmarketing Experience

Ertapenem was recently approved for marketing in Brazil and Mexico; however, no postmarketing information is available at this time.

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V. Clinical Review Methods

5.1 Approach to Clinical Review

Data in support of each of the indications sought by the Applicant were reviewed separately for efficacy and safety. Dr. Thomas Smith reviewed data related to the complicated urinary tract infections indication and Dr. Janice Pohlman reviewed data related to the complicated skin and skin structure indication. Dr Jean Mulinde reviewed data related to the complicated intra-abdominal infections indication, the acute pelvic infections indication, and the community acquired pneumonia indication. In depth reviews of all pivotal Phase IIb and III studies, in support of the requested indications, are contained in sections VI and VII of this review. Results of Phase I and Phase IIa studies are commented on where appropriate. In addition, an Integrated Safety Review was performed in which safety data from all Phase I, IIa, IIb, and III studies were reviewed, and is included in section VII of this review.

5.2 Materials Consulted in Review

In addition to the electronically submitted materials in NDA 21,337, past and current submissions to [redacted] were evaluated and commented on, where appropriate in this review. Literature reviewed is noted in footnotes throughout the review.

5.3 Methods of Data Quality and Integrity Evaluation

DSI audits were performed at six clinical trial sites and did not reveal any significant deficiencies or discrepancies that would invalidate the studies. A summary of audited sites is displayed in the following table.

Investigator	Location	Protocol	Patients Enrolled
Alvaro Francisco Fernandez Garcia, MD	Guatemala	017	50
Elliot Frank, MD	Neptune, NJ	014	26
Donald R. Graham, MD	Springfield, IL	018	14
Christopher Lucasti, DO	Somers Point, NJ	016	57
Nora Quintero Prez, MD	Mexico	017	41
Subir Roy, MD	Los Angeles, CA	016	30
		023	37

In addition to the DSI audits, clinical reviewers reviewed at least 10% of the Case Report Forms, for each of the pivotal Phase IIb/III studies, for concurrence with the Applicant's evaluability and outcome assessments and database quality. The Applicant's statistical analyses were reviewed and confirmed by Dr. Joel Jiang and Dr. George Rochester. Discrepancies that were identified by the FDA review team were discussed with the Applicant.

5.4 Ethical Standards

According to documentation provided by the Applicant, for all clinical studies:

- Investigators were "responsible for obtaining Review Board approval of the protocol, as well as approval of all subsequent major changes, in compliance with local law."
- Studies were "conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research."
- All Investigators were "responsible for obtaining documented consent from each potential study patient before the administration of the first dose of study drug. Consent was documented by the patient's dated signature on a Consent Form along with the dated signature of the person conducting the consent discussion. For non-English-speaking patients, a translated consent form was provided with a written statement by the translator, indicating that the consent form was an accurate translation of the accompanying English version. "

Based on DSI audits and the Medical Officers' reviews of Case Report Forms it appears that these ethical standards were adhered to.

5.5 Evaluation of Financial Disclosure

The Applicant certified that they have not entered into any financial arrangement with their clinical investigators that could affect the outcome of the studies. They have provided a listing of all investigators/subinvestigators that were certified by Merck regarding the absence of financial arrangements as defined in 21 CFR 54.2. They have also provided a table of all investigators/subinvestigators for whom financial interest disclosure was required (See Volume 1 of 1, page 113, original NDA submission). In addition, for those investigators/subinvestigators for whom the Applicant could not provide complete financial disclosure information, the Applicant certified that despite attempting to obtain the information with due diligence, they were unable to and they have provided an explanation of how attempts were made and why the information was not obtainable.

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VI. Integrated Review of Efficacy

6.1 Complicated Intra-Abdominal Infections Indication

6.1.1 Reviewer: Jean M. Mulinde
Medical Officer, HFD-520

6.1.2 Indication Review Dates

6.1.2.1 Received by reviewer: December 5, 2000

6.1.2.2 Review begun: February 20, 2001

6.1.2.3 Review completed: July 19, 2001

6.1.2.4 Review revised: September 18, 2001

6.1.3 Indication Specific Proposed Label Claims and Critical Differences From Applicant's Proposed Label Claims

The Applicant has proposed the following label claims in reference to the complicated intra-abdominal infections indication:

- In the **INDICATIONS AND USAGE** section of the label.

"Complicated Intra-abdominal Infections due to: Escherichia coli,
Eubacterium species, Peptostreptococcus species, Bacteroides

And at the end of the entire section, as a separate paragraph:

Medical Officer's Comment: Based on the MO review that follows the MO recommends that this section be amended to the following:

**"Complicated Intra-abdominal Infections due to *Escherichia coli,*
Clostridium clostridiiforme, Eubacterium lentum, Peptostreptococcus species,
Bacteroides fragilis, Bacteriodes distasonis, Bacteriodes ovatus, Bacteriodes
thetaiotaomicron, or Bacteriodes uniformis."**

The separate paragraph above should be completely removed from the label. The Applicant has not provided adequate data to support bacteremia claims for complicated intra-abdominal infections or acute pelvic infections. Statements regarding E. coli bacteremia in patients with complicated urinary tract infections and S. pneumoniae in patients with community acquired pneumonia should be incorporated into the specific indication statements.

6.1.5 PROTOCOL 017: A PROSPECTIVE, MULTICENTER, DOUBLE-BLIND, RANDOMIZED, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF MK-0826 VERSUS PIPERACILLIN-TAZOBACTAM IN THE TREATMENT OF COMPLICATED INTRA-ABDOMINAL INFECTIONS IN HOSPITALIZED ADULTS

6.1.5.1 Objective/Rationale

The objectives of the study, as stated by the Applicant, were:

Primary Objectives

1. To compare the efficacy of MK-0826 with respect to both the clinical response assessment profile and the microbiologic assessment profile in the treatment of patients with complicated IAIs with that of piperacillin/tazobactam at the 4- to 6-week posttreatment follow-up visit.
2. To evaluate the safety profile of MK-0826 versus piperacillin/tazobactam with respect to the proportion of patients with any drug-related adverse experiences leading to discontinuation of study drug and also with respect to the proportion of patients with any drug-related serious adverse experience.

Secondary Objectives

1. To compare the efficacy of MK-0826 with respect to both the clinical response assessment profile and the microbiologic assessment profile in the treatment of patients with complicated IAIs with that of piperacillin/tazobactam at the time of discontinuing IV therapy, and at the early follow-up visit at 1 to 2 weeks posttreatment.
2. To compare the efficacy of MK-0826 with respect to the clinical response assessment profile in the treatment of patients with complicated IAIs with that of piperacillin/tazobactam at each time point.
3. To compare the efficacy of MK-0826 with respect to the microbiologic response assessment profile in the treatment of patients with complicated IAIs with that of piperacillin/tazobactam at each time point.
4. To determine the tolerability profile of intravenous MK-0826 in patients with complicated IAIs as compared with piperacillin/tazobactam.
5. At selected sites, to evaluate the drug levels in patients at 6 and 12 hours postdose on Day 3 of IV therapy for pharmacodynamic analysis.

Tertiary Objectives

1. To compare the efficacy of MK-0826 with respect to clinical and microbiologic assessment profile as compared to piperacillin/tazobactam in the treatment of infections caused by ESBL producing organisms.
2. To determine the in vitro activity of MK-0826 against clinical isolates expressing ESBLs.

***Medical Officer's Comment:** The secondary objective to evaluate drug levels was dropped by the Applicant because an adequate number of samples were not available due to inadequate sample storage procedures. Both of the tertiary objectives were dropped by the Applicant due to the small number of patients with ESBL producing pathogens that were enrolled in the study.*

6.1.5.2 Design

This was a prospective, multicenter, double-blind, randomized, comparative study conducted at 26 centers in the United States and 31 centers internationally. Twenty-one centers in the United States and 30 centers internationally (9 from Latin America; 14 from Eastern and Western Europe; 4 from Canada; and 3 from South Africa) actually enrolled patients between April 1998 and October 15, 1999.

Following presumptive or definitive diagnosis of IAI, eligible patients were stratified at study entry for balance between the treatment groups based on site of infection (diagnosis of complicated appendicitis versus all other eligible diagnoses) and by disease severity (APACHE II score ≤ 15 or > 15). Stratified patients were then randomly assigned to receive ertapenem once daily (the dose of MK-0826 was changed from 1.5 to 1 gm daily when supportive evidence for the 1 gm dose was obtained from study 004) or piperacillin/tazobactam 3.375 gm every 6 hours (1:1 ratio). Each treatment regimen was to be administered for a minimum of 5 days and a maximum of 14 days.

Patients were required to have a surgical procedure or radiologic intervention within 24 hours of enrollment to provide documentation of complicated IAI and to allow determination of etiologic pathogens. Cultures (aerobic and anaerobic) were performed at prestudy and with any subsequent operative or radiologic intervention as clinically indicated. If no admission pathogen was isolated, the patient remained in the study for clinical evaluation. If the admission culture was known prior to enrollment to contain a pathogen resistant to either study drug, the patient should not have been enrolled in the study. If the baseline pathogen (unknown at study entry) was found during the study to be resistant to either of the study drugs, and there was no clinical improvement, the patient should have been discontinued as a failure; however, if the patient was improving, the patient was allowed to remain in the study at the discretion of the investigator. Vital signs and a detailed abdominal assessment were performed at prestudy, daily during study antibiotic therapy, at the discontinuation of the study treatment, at the early follow-up (EFU) visit, 7 to 14 days post completion of study therapy and at the late follow-up (LFU) visit, 4 to 6 weeks post completion of study therapy.

The safety of parenteral MK-0826 and of parenteral piperacillin/tazobactam was evaluated by determining the presence or absence of clinical or laboratory adverse experiences. Patients were monitored for adverse experiences on a daily basis during the parenteral study antibiotic period and for 14 days after the discontinuation of study therapy. Adverse experiences of special interest, identified by the Applicant, included: seizures (regardless of prior seizure history); elevated transaminases; neutropenia; and rash of sufficient severity to

require discontinuing study antibiotic. The schedule of clinical observations and laboratory measurements is in Appendix 1.

At the late follow-up visit (TOC visit), 4 to 6 weeks after completion of study antibiotic therapy, clinical efficacy was determined based upon the investigator's assessment of the overall clinical response to therapy. Microbiological efficacy for each pathogen was determined based upon the results of bacterial cultures and was correlated with the clinical response. An expert review panel composed of investigators and non-investigators was convened to assess adequacy of surgical source control in clinical failures. In addition, the panel reviewed the assessment of "cure" for patients who had additional surgical interventions before the TOC visit, to determine whether there was evidence of clinical failure at the time of the re-intervention. This 2-stage review was conducted on blinded data, and the conclusions of the panel were implemented in the database and in all analyses.

Medical Officer's Comment: *It is notable that the protocol design did not allow a switch to oral antimicrobial therapy.*

It is also notable that the protocol was amended during the course of the study to provide additional blinding procedures when it was recognized that a slight color difference could sometimes be detected between MK-0826 and placebo. Measures implemented by the Applicant to assure the study drug blind was maintained included: limits on the time of reconstitution; limits on the choice of the final infusion container; prompt disposal of study infusion bags after use; and the use of amber-colored translucent bag covers.

6.1.5.3 Protocol Overview

6.1.5.3.1 Population/Procedures

Inclusion and exclusion criteria were applied in order to enroll patients with complicated IAI that were likely to be treatable with the initial surgical procedure and parenteral therapy of no more than 14 days duration. The following are noteworthy inclusion and exclusion criteria:

Noteworthy Inclusion Criteria:

A. Intraoperative/Postoperative Enrollment

Patients may have been enrolled intraoperatively or postoperatively upon visual confirmation (presence of pus within the abdominal cavity) of an IAI. Surgical intervention included open laparotomy, laparoscopic surgery, or percutaneous drainage of an abscess. The initial intervention should have been adequate, a procedure in which all communications between the gastrointestinal tract and the peritoneal cavity were closed and no necrotic intestine was left, and all infected collections were drained at the initial procedure.

Diagnoses considered eligible for this study were those in which there was evidence of intraperitoneal infection. These include the following:

1. Cholecystitis (including gangrenous) and either rupture, perforation, or progression of the infection beyond the gallbladder wall.
2. Diverticular abscess.
3. Appendiceal perforation and periappendiceal abscess.
4. Acute gastric and duodenal perforations, only if operated on >24 hours after perforation occurred.
5. Traumatic perforation of the intestines, only if operated on >12 hours after perforation occurred.
6. Peritonitis due to perforated viscus, postoperative or other focus of infection (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites).
7. Intra-abdominal abscess (including liver and spleen).

NOTE: (a) Patients with infections limited to the hollow viscus, such as simple cholecystitis and simple appendicitis, were not eligible. Patients with ischemic bowel disease without perforation were not eligible. Patients with acute suppurative cholangitis and acute necrotizing pancreatitis were not eligible because the primary intervention in the former is Endoscopic Retrograde Cholangio-Pancreatography (ERCP), and for the latter a single operative intervention is not definitive. (b) Postoperative (or intraoperative) enrollment of patients was encouraged. If, however, preoperative data were available that strongly suggested an appropriate diagnosis for entry (e.g., intraperitoneal abscess on computed tomography [CT] scan), then these patients could have been enrolled preoperatively.

B. For Preoperative Enrollment

A patient may have been enrolled preoperatively if the following clinical criteria were met, and if the patient's infection was confirmed by a surgical intervention within 24 hours of entry:

1. Evidence of a systemic inflammatory response, with at least one of the following:
 - a. fever (temp $\geq 100.0^{\circ}$ F oral; $\geq 100.4^{\circ}$ F tympanic; $\geq 100.8^{\circ}$ F rectal)
 - b. elevated white blood cell count (WBC) ($\geq 10,500/\text{mm}^3$)
 - c. drop in blood pressure (systolic blood pressure must have been >90 mm Hg without the need for pressor support)
 - d. increased pulse and respiratory rates
 - e. hypoxemia
 - f. altered mental status

and

2. Physical findings consistent with IAI, such as:
 - a. abdominal pain and/or tenderness
 - b. localized or diffuse abdominal wall rigidity
 - c. mass

d. ileus

and

3. Supportive radiologic findings in abdomen such as intraperitoneal abscess detected on CT scan films

and

4. Requirement for surgical intervention, including open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery.

C. Other Inclusion Criteria

1. Specimens from the surgical intervention were sent for culture and susceptibility testing.
2. Infection was caused or presumed to be caused by microorganisms susceptible to the intravenous study antibiotics (MK-0826 and piperacillin/tazobactam).
3. Patient was an adult (male or female) ≥ 18 years of age.
4. Females of childbearing potential must have had a negative serum

pregnancy test (β -human chorionic gonadotropin [β -hCG]) prior to enrollment into the study and, subsequently, for at least 1 month after study treatment must have agreed to use adequate birth control measures as discussed with the investigator. Hormonal contraceptives were not to be used as the sole method of birth control, because the effect of MK-0826 on the efficacy of hormonal contraceptives had not been established.

Notable Exclusion Criteria

1. Diagnosis of traumatic bowel perforation with surgery within 12 hours; perforation of gastroduodenal ulcers with surgery within 24 hours (these were considered situations of peritoneal soiling before infection had become established). Other intra-abdominal processes in which the primary etiology was not likely to be infectious.
2. Simple cholecystitis; gangrenous cholecystitis without rupture; simple appendicitis; acute suppurative cholangitis; infected, necrotizing pancreatitis.
3. Patients that were to be managed by Staged Abdominal Repair (STAR) or open abdomen technique.
4. Patients known at study entry to have IAIs that were caused by pathogens resistant to the study antimicrobial agents.
5. APACHE II score >30 .
6. Patients who were considered unlikely to survive the 6- to 8-week study period.
7. The need for concomitant systemic antimicrobials (other than vancomycin or antifungal agents) in addition to those designated in the 2 study groups.

8. Patients with creatinine clearance ≤ 30 mL/min, or those requiring peritoneal dialysis, hemodialysis, or hemofiltration were excluded.
9. The presence of hepatic disease:
 - a. Alanine transaminase [ALT], aspartate transaminase [AST] $> 6 \times$ upper limit of normal (ULN) values used by the laboratory performing the test. Patients with elevations of AST and/or ALT up to $10 \times$ ULN were allowed if these elevations were acute and directly related to the infectious process being treated.
 - b. Bilirubin $> 3.0 \times$ ULN, unless isolated hyperbilirubinemia was directly related to the acute process.
 - c. Alkaline phosphatase $> 3.0 \times$ ULN. Patients with values $> 3.0 \times$ ULN and $< 5.0 \times$ ULN were eligible if this value was historically stable.
 - d. Patients with acute hepatic failure or acute decompensation of chronic hepatic failure should have been excluded.
10. Hematocrit $< 25\%$ or hemoglobin < 8 g/dL.
11. Neutropenia with absolute neutrophil count (ANC) $< 1000/\text{mm}^3$. Patients with neutrophil counts as low as 500 cells/ mm^3 were permitted if this reduction was due to the acute infectious process.
12. Platelet count $< 75,000/\text{mm}^3$. Patients with platelet counts as low as $50,000$ cells/ mm^3 were permitted if this reduction was historically stable.

13. Coagulation tests $> 1.5 \times$ ULN (prothrombin time [PT] and partial thromboplastin time [PTT] and/or international normalization ratio [INR]). Patients on anticoagulant therapy with values $> 1.5 \times$ ULN could have been enrolled, provided these values were stable and within the therapeutic range.
14. Immunosuppressive therapy, including use of high-dose corticosteroids (e.g., 40 mg or more prednisone or equivalent per day) or diagnosis of Acquired Immunodeficiency Syndrome.

***Medical Officer's Comment:** The Applicant's inclusion and exclusion criteria are acceptable and in general accordance with recommendations in the 1992 FDA Points to Consider for Clinical Development and Labeling of Anti-Infective Drug Products and with the IDSA's 1992 Guidelines for the Evaluation of New Anti-Infective Drugs for the Treatment of Intraabdominal and Pelvic Infections².*

6.1.5.3.2 Evaluability Criteria

According to the Applicant, determinations of evaluability for the per protocol and MITT populations were made prior to unblinding using the prespecified criteria stated in the Data Analysis Plan (DAP). The following criteria were used by the Applicant to define study populations for analysis:

Screened population

All patients who signed a consent form for the study. This population includes those patients who were not randomized to therapy and those patients who were randomized to therapy.

² Solomkin et al., Clinical Infectious Diseases 1992;15(Suppl. 1):S33-42.

Randomized population

A subset of the screened population comprised of patients who were randomized to a study regimen, irrespective of whether the patient actually received therapy. Patients randomized to 1 treatment group who, due to dispensing errors, mistakenly received study therapy with the other study treatment for the entire parenteral study period were analyzed and displayed throughout based on the study therapy actually received. Patients who, due to dispensing errors, received both parenteral study drugs at any time during the course of the study were analyzed for demographics and safety based on the treatment group to which they were originally randomized, but were not included in any efficacy analyses.

Treated population

A subset of the randomized population comprised of patients who received at least 1 dose of study therapy. Only treated patients are included in the analysis of safety.

Clinical MITT population

A subset of the treated population comprised of patients that met the minimal disease definition.

Microbiologic MITT population

A subset of the clinical MITT population comprised of those clinical MITT patients who had a baseline pathogen identified, regardless of susceptibility to study agents, and a microbiologic response assessed.

Clinically evaluable population

A subset of the clinical MITT population comprised of patients for whom sufficient information was available to determine the patients' outcome and no confounding factors were present that interfered with the assessment of that outcome; furthermore, it was required that if baseline pathogens were identified, one or more of these pathogens were susceptible to both parenteral study therapies.

Study specific criteria for the IAI indication that were provided in the Applicant's DAP required that the patient meet the clinical, radiographic, and microbiologic criteria as specified in the inclusion criteria. The following additional criteria were also provided in the DAP:

- 1) The test-of-cure visit is 21-52 days after the end of study therapy.
- 2) Patients should have received $\geq 80\%$ of the intended doses to be considered evaluable. MK-0826 is administered once per day as dose "A" and piperacillin/tazobactam is administered four times a day as doses "A", "B", "C", and "D". Therefore, in the blinded preliminary assessment patients must receive $\geq 80\%$ of the intended "A" doses and $\geq 80\%$ of the intended "A", "B", "C", and "D" doses. In the unblinded confirmatory assessment, patients must receive $\geq 80\%$ of the intended doses of randomized therapy.

- 3) Patients must receive ≥ 4 and ≤ 17 d of total study therapy to be considered an evaluable success. Patients must receive > 48 hours of parenteral therapy to be considered an evaluable failure.

The DAP also included the following "Evaluability exclusions" for the IAI study:

- 1) Exclusions resulting from prior antimicrobials
 - a) ≥ 24 h appropriate systemic antimicrobial therapy prior to enrollment unless there is evidence of clinical failure with a persistent pathogen. Evidence of failure requires a new surgical procedure with positive cultures: failures of either medical and/or surgical therapy are acceptable.
 - b) More than one post-operative dose of antimicrobials (either a single agent or a regimen) following the procedure at which the entry culture was obtained.
- 2) Exclusions resulting from concomitant antimicrobials
 - a) Use of more than one dose of a non-study systemic antimicrobial with activity against the pathogen under study for reasons other than clinical failure. If a non-study systemic antimicrobial with activity against the pathogen under study is used after study therapy is completed and the patient is subsequently a clinical failure prior to or at the test-of-cure visit, then the patient can still be a "protocol-evaluable" failure. Vancomycin for MRSA or enterococci in mixed infections is acceptable but renders all gram positive pathogens of the mixed infection indeterminate. Low dose erythromycin, 125 mg b.i.d., as a promotility agent is acceptable. Standard prophylactic antimicrobials for post-entry re-operation or interventions that are not due to infection are acceptable (e.g. colonic reanastomosis after colostomy). A switch to non-study therapy will be considered an evaluable failure if clinical signs of ongoing intra-abdominal infection are present or non-evaluable if there are no signs of ongoing intra-abdominal infection. Patients, however, who receive additional antimicrobial agents for nosocomial infections or other infections outside of the abdomen ≥ 5 days into the study should be evaluated on the day upon which therapy with these agents is initiated. If there is no evidence of intra-abdominal sepsis at this time, and there is no evidence of recurrent intra-abdominal infection during the subsequent clinical course, then the patients are considered to be evaluable as clinical cures.³
- 3) Exclusions due to baseline or intercurrent medical events
 - a) Patients must not have any of the following at the time of study entry or within 48 hours of admission:
 - i) Infections excluded at baseline:
 - a) Simple cholecystitis (gangrenous gallbladder and empyema of gallbladder are acceptable).
 - b) Simple appendicitis.
 - c) Acute suppurative cholangitis.

³ Solomkin et al., Clinical Infectious Diseases 1992;15(Suppl.1):S33-42.

- d) Infected, necrotizing pancreatitis (infected pseudocysts or pancreatic abscess, for example, are not excluded).
- ii) Patient was managed by staged abdominal repair procedure (STAR)
- iii) No evidence of intra-abdominal and/or intra-pelvic infection
- iv) absolute neutrophil counts <500 cells/mm³ prior to therapy
- b) Patients must not have had any of the following at study entry through the test-of-cure visit if they interfere with evaluation of the response to study therapy:
 - i) Concurrent infection.
 - ii) Concurrent surgical or medical condition.
 - iii) Chronic immunosuppressive therapy (chemotherapy/immunosuppressants or prednisone >40 mg/d or its equivalent) or AIDS; HIV-infection without AIDS is acceptable.
- 4) Exclusion due to baseline microbiology
 - a) isolation of a sole aerobic pathogen not susceptible (I or R) to either parenteral study drug.

Microbiologically evaluable population

A subset of the clinically evaluable population comprised of those clinically evaluable patients who had a baseline pathogen identified and a microbiologic response assessed. As all microbiologically evaluable patients were required to be clinically evaluable, the population of clinically and microbiologically evaluable patients was identical to the microbiologically evaluable population; for all data presented hereafter, this group is referred to as the microbiologically evaluable population.

The Applicant's DAP also required that for Protocol 017 microbiologic evaluability that "patients must have an aerobic pathogen isolated from a pre-study culture that is susceptible to both MK-0826 and comparator, or an anaerobe, in which case susceptibility data are not required. Patients must have at test-of-cure either a microbiology specimen collected or be presumed eradicated/persistent."

Medical Officer's Comment: *The MO feels that several of the criteria, regarding concomitant antimicrobials, used by Applicant to determine the Clinical Evaluable Population are inappropriate. The criteria that the MO is in disagreement with are:*

1. *"Standard prophylactic antimicrobials for post-entry re-operation or interventions that are not due to infection are acceptable (e.g. colonic reanastomosis after colostomy)." The statement does not specify whose standard will be used (individual investigator standards vs professional society recommendations versus "standard of care"), resulting in some patients being considered evaluable after prolonged courses of "prophylactic" antibiotics. This issue was not previously raised with the Applicant during DAP discussions prior to the NDA submission.*
2. *"A switch to non-study therapy will be considered an evaluable failure if clinical signs of ongoing intra-abdominal infection are present, or non-evaluable if there are no signs of ongoing intra-abdominal infection." This criterion was discussed during the DAP discussions at the December 21, 1999 teleconference between the Applicant and the Division. The Applicant was informed that since the protocol was designed as an IV therapy only study, with no switch to oral therapy allowed,*

- that the Division would consider all patients that Investigators thought required additional oral antimicrobial therapy (to treat the intra-abdominal infection) to be evaluable failures.
3. "Patients, however, who receive additional antimicrobial agents for nosocomial infections or other infections outside of the abdomen ≥ 5 days into the study should be evaluated on the day upon which therapy with these agents is initiated. If there is no evidence of intra-abdominal sepsis at this time, and there is no evidence of recurrent intra-abdominal infection during the subsequent clinical course, then the patients are considered to be evaluable as clinical cures." The Applicant has footnoted this criterion with a citation for the IDSA guidelines for treatment of intra-abdominal infections; however, those guidelines do not state patients should be "considered to be evaluable as clinical cures" but, rather state this group of patients should be "considered to be clinically cured," with no mention of how to handle evaluability. In addition, from a regulatory perspective it is problematic to assign an outcome of cure to a patient who has been given additional non-study antimicrobials that have efficacy against pathogens in the index infection, since these antimicrobials may be adequate to prevent relapse in patients that would otherwise clinically relapse. This issue was not previously raised with the Applicant during DAP discussions prior to the NDA submission.

The MO has used to the following revised criteria for the 3 groups above:

1. Unless the patient was considered unevaluable for some other reason, a patient who received ≤ 24 hours of an antimicrobial agent for post-entry re-operation or interventions that are not due to infection (e.g. colonic reanastomosis after colostomy) may be considered evaluable.
2. Unless the patient was considered unevaluable for some other reason, a patient that received non-study antimicrobial therapy, for continued treatment of the intra-abdominal infection, at the end of the IV study drug period was considered an evaluable failure.
3. A patient that received a non-study antimicrobial to treat an infection unrelated to the study entry index infection, prior to the TOC visit, was considered unevaluable with an indeterminate outcome.

6.1.5.3.3 Endpoints

The Applicant provided the following endpoint definitions:

Clinical Response

A favorable clinical response assessment was "cure" at the discontinuation of IV therapy (DCIV), early follow-up 1 to 2 weeks post-therapy (EFU), and LFU (TOC) visits. Once a patient had an "unfavorable" clinical assessment, the patient was counted as having that "unfavorable" response at all subsequent time points.

The definitions of the Applicant's clinical responses assigned were:

Clinical Response Definitions

Clinical Response	Definitions
Cure	Resolution of the index infection. No further antimicrobial therapy is necessary.
Failure	<ol style="list-style-type: none"> a. Death related to intra-abdominal infection at any time point. b. Persisting or recurrent infection within the abdomen documented by the findings at re-intervention either percutaneously or operatively c. Postsurgical wound infection, or d. Patients who received treatment with additional antibiotics for undocumented intra-abdominal infection during the study period.
Indeterminate	<p>Study data were not available for evaluation of efficacy for any reason, including:</p> <ol style="list-style-type: none"> a. Death occurred during the study period and the index infection was clearly noncontributory b. Extenuating circumstances precluded classification as cure or failure.

(Applicant's Table 5, Volume 13 of 22, page 59)

Microbiological Response

At the TOC visit, an overall microbiological response was assessed as "favorable" or "unfavorable" for each patient. Favorable microbiological response assessments were "eradication" and "presumptive eradication". For patients from whom only 1 pathogen was isolated, the overall microbiological response assessment was based on the microbiological response assessment for that pathogen. For patients from whom more than 1 baseline pathogen was isolated, the overall microbiological response assessment reflected the worst microbiological outcome for all baseline pathogens. For a favorable overall microbiological assessment, each pathogen identified at baseline must have had a favorable or indeterminate response assessment.

The definitions of microbiological responses assigned by the Applicant at each study visit were:

Microbiological Response Definitions

Microbiological Response	Definitions
Eradication	Absence of all causative organisms at the end of therapy.
Presumptive eradication	Absence of material to culture in a patient who had responded clinically to treatment.
Persistence	Any causative organism still present at or beyond the end of therapy from a culture of intra-abdominal abscess, peritonitis, or surgical wound infection.
Persistence acquiring resistance	Continued presence of the original pathogen in cultures from the original site of infection obtained during or upon completion of therapy, and the pathogens that were susceptible, moderately susceptible, or intermediate to study drug pretreatment had become resistant to study drug therapy posttreatment.
Presumed persistence	Repeat cultures were not obtained because of the absence of material to culture in a patient who was given additional antibiotic treatment for abdominal infection.
Superinfection	Emergence of new pathogen during therapy, either at the site of infection or at a distant site with emergence or worsening of signs and symptoms of infection.
New infection	Eradication of the original pathogen followed by replacement (at the same site and after completion of therapy) by a new species or by a new serotype or biotype of the same organism in the presence of signs or symptoms of infection.
Indeterminate	<ul style="list-style-type: none"> a. Entry culture either not obtained or no growth. b. Assessment not possible because of protocol violation. c. Any other circumstance that made it impossible to define the microbiological response.

(Applicant's Table 6, Volume 13 of 22, page 60)

Medical Officer's Comment: *The Applicant's endpoint definitions are acceptable and in general accordance with recommendations in the 1992 FDA Points to Consider for Clinical Development and Labeling of Anti-Infective Drug Products and with the IDSA's 1992 Guidelines for the Evaluation of New Anti-Infective Drugs for the Treatment of Intraabdominal and Pelvic Infections⁴.*

⁴ Solomkin et al., Clinical Infectious Diseases 1992;15(Suppl. 1):S33-42.